Claim Rejections - 35 USC §112, Second Paragraph

Claims 3, 5, 6, 14 and 16-28 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that the phrase "minimally complementary" is indefinite because the specification fails to define this term and because no objective criterion is provided in the specification or in the claims which appraises the skilled artisan of the meaning of this term.

Applicant respectfully traverses the rejection. Applicant notes that the phrase "minimally complementary" is defined on pages 23-24 of the specification and describes the condition of two single stranded nucleic acids which are sufficiently complementary to hybridize or anneal to one another under at least low stringency conditions given that the two nucleic acid strands exhibit roughly 10 to 30 or 40% mismatches, but remain sufficiently complementary to allow for strand annealing in the presence of Rad52 protein. Applicant further notes that the term "minimally complementary" is routinely and widely used in the art and the ordinarily skilled artisan would readily recognize the term. Applicant, therefore, respectfully requests reconsideration and withdrawal of the outstanding rejection.

Claim Rejections - 35 USC §112, Second Paragraph–Omission of Essential Step

Claims 14, 16, and 18-20 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being incomplete for omitting essential steps where such omission amounts to a gap between the steps. Examiner states that the omitted step is "(b) screening for altered activity" since there is no recitation step in the claims which indicates the nature of the activity or the manner in which the previous combining steps leads to an activity which can be measured.

Applicant respectfully traverses the rejection and argues the following:

The activity to be measured in claim 14 is the nucleic acid binding activity exhibited by the candidate bioactive agent upon contacting (step a) ss DNA and Rad52 protein.

The activity to be measured in claim 16 is the nucleic acid and/or protein-to-protein binding activity exhibited by the candidate bioactive agent upon being added (step a) to a mixture containing ss DNA and Rad52.

The activity to be measured in claim 18 is the nucleic acid and/or protein-to-protein binding activity exhibited by the candidate bioactive agent upon being added (step a) to a mixture containing ss DNA and Rad52.

The activity to be measured in claim 19 is the nucleic acid and/or protein-to-protein binding activity exhibited by the candidate bioactive agent upon being added (step a) to a mixture containing ss DNA and Rad52.

The activity to be measured in claim 20 is the nucleic acid and/or protein-to-protein binding activity exhibited by the candidate bioactive agent upon being added (step a) to a mixture containing ss DNA and Rad52.

Applicant, therefore, respectfully requests reconsideration and withdrawal of the outstanding rejection.

Claim Rejections - 35 USC §102(b) As Being Anticipated by *Shinohara*

Claims 1 is rejected under 35 U.S.C. §102(b) as being anticipated by *Shinohara et al.*

Claim 1 recites a composition which comprises a first and second single stranded nucleic acids which are complementary to each other, and at least one recombinant Rad52 protein from a higher eukaryote.

Applicant notes that *Shinohara et al.* is primarily directed to a discussion of the proteins derived from bacteria (prokaryote) and yeast (a single-celled simple eukaryote) which participate in recombination and repair mechanisms. The Examiner specifically directs Applicant to the section entitled "Complexes Involved in the Formation and Repair of DSBs." The Rad52 protein taught in this section has been purified from *S. cerevisiae* (yeast) and participates in the formation of double-stranded breaks and subsequent processing of yeast DNA. The recombinant Rad52 protein claimed in Applicant's composition, conversely, was not purified from yeast, did not originate from a simple eukaryote, and the chemical composition does not participate in the breakage of DNA strands.

Further, although *Shinohara* teaches that human and yeast Rad52 exhibit some homology (60%) at their amino terminal ends, partial homology of proteins does not dictate identical or similar function. In homologous recombination processes, it is the non-conserved carboxyl-terminal region of eukaryotic Rad52 that actually binds to eukaryotic Rad51 in a species-specific manner. *Shinohara*, itself, even states that eukaryotic recombination and repair mechanisms involve proteins which participate in a myriad of different protein complexes and that the processes by which these various protein complexes are formed and the manner in which they function in recombination mechanisms will not be understood until a eukaryotic *in vitro* system has been established (p.391).

In any case, because the *Shinohara* protein is from a lower eukaryote, it is not within the scope of Applicant's claim. For these reasons, it is not proper for the Examiner to assume equivalency of function or of identity between the Rad52 of higher eukaryotes claimed by Applicant's invention and the yeast Rad52 protein taught in *Shinohara*.

For these reasons, the Examiner's rejection under 35 U.S.C. §102(b) of claim 1, and claims 2,4,5,23,24,25 and 26 which depend therefrom, should be withdrawn.

The Examiner additionally states that Applicant's method claims (Claims 14,16, 17,18,19,20,21, and 22) are rejected under 35 U.S.C. §102(b) as being anticipated by *Shinohara*. Applicant respectfully traverses the rejection. Applicant's claims teach of a method for screening a single candidate bioactive agent in which a single stranded nucleic acid and an isolated Rad52 protein from a higher eukaryote are associated. *Shinohara,* in contrast, teaches of a yeast RPA protein which initially binds the 3' end of yeast ssDNA. The bound RPA subsequently associates with yeast Rad52. Upon complexing with RPA, Rad52 then recruits and complexes with another yeast protein, Rad51. Each of Applicant's method claims teaches of a Rad52 protein that is isolated from a higher eukaryote, more specifically, from a mammal (claim 21) or most specifically, from a human (claim 22). The Rad52 taught in *Shinohara* has been purified from *S. cerevisiae*. *S. cerevisiae* is a yeast, it is not a higher eukaryote. The yeast Rad52 taught in *Shinohara* is therefore not the same protein that is claimed by Applicant. Further *Shinohara* does not teach a method for screening a single bioactive agent. *Shinohara* merely describes an observable natural mechanism by which two

yeast proteins, in addition to yeast Rad52, associate, sequentially, *in vivo*, in a particular configuration, with single stranded yeast DNA. Applicant's method screens for candidate bioactive agents, requires only a single DNA bound protein (Rad52) for utility, does not require practice within a living yeast cell, and does not require that higher eukaryotic Rad52 bind to either single stranded nucleic acid or to the candidate bioactive agent in any particular sequential order or configuration, for utility. For the foregoing reasons, the Examiner's rejection under 35 U.S.C. §102(b) of claims 14,16, 17,18,19,20,21, and 22 should be withdrawn.

Claim Rejections - 35 USC §102(b) As Being Anticipated by *Park*

The Examiner finally argues that Applicant's claim 1 is rejected under 35 U.S.C. §102(b), as being anticipated by *Park*.

The examiner states that *Park* teaches a composition comprising a first single stranded nucleic acid, a perfectly matched or partially matched second single stranded nucleic acid, and a human Rad52 protein from a higher eukaryote.

Applicant respectfully traverses the Examiner's rejection.

Applicant argues that although the *Park* reference describes the cloning and characterization of a human Rad52 cDNA, it does not teach a specific nucleoprotein complex that is comprised of two single complementary strands of nucleic acid which bind to a specific recombinant protein where such nucleoprotein complex is designed to perform a particular biological task. The *Park* reference merely describes the manner in which homologous recombination can be induced by exposing monkey cells, which exhibit overexpression of human Rad52, to radiation. Although *Park* describes certain recombination activities which take place in these monkey cells, and these activities obviously involve numerous associations of proteins with nucleic acids, the reference does not teach of a specific combination of nucleic acid and protein elements which are added together for the purpose of screening for candidate bioactive agents. Therefore, although the *Park* reference describes a complex process taking place within a cell and that process involves the participation of numerous proteins in association with various nucleic acid strands, which may or may not be complementary to one

other, the reference does not teach a specific nucleoprotein combination whose formation is engineered to perform a particular function. In sum, the cellular processes described in *Park* are not within the scope of Applicant's claims.

For these reasons, the Examiner's rejection under 35 U.S.C. §102(b) of claim 1, and claims 4,5,23, and 26 which depend therefrom, must be withdrawn.

Compliance with 37 C.F.R. § 1.821-1.825

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Entry of this amendment is respectfully requested. The amendments are made in adherence with 37 C.F.R. § 1.821-1.825. This amendment is accompanied by a floppy disk containing the above named sequence, SEQUENCE ID NUMBERS 1-2, in computer readable form, and a paper copy of the sequence information. The computer readable sequence listing was prepared through use of the software program "PatentIn" provided by the PTO. The information contained in the computer readable disk is identical to that of the paper copy. This amendment contains no new matter. Applicant submits that this amendment, the accompanying computer readable sequence listing, and the paper copy thereof serve to place this application in a condition of adherence to the rules 37 C.F.R. § 1.821-1.825.

Based upon the foregoing, it is submitted that claims 1-3; 5-6; 14; 16-26; and 28 are patentable over the art of record.

The Commissioner is authorized to charge any additional fees including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-64077-2/RFT/RMS/BTC).

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and an early notification of such is solicited. If, upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Date: September 26, 2001

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VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 26, line 24, has been amended as follows:

– **Cloning of the HsRad52 gene.** The whole coding sequence of human Rad52 (HsRad52) was amplified by PCR from human thymus cDNA library. Sequences of the upstream and downstream primers are EG182: CGCGGATCCGATGTCT GGGACTGAGGAAGCAA (SEQ ID NO:1) and EG225: GTAGGATCCTGAGCCTCAGTTAAG ATGG (SEQ ID NO:2). Underlined sequences are homologous to the published 5' end and 3' end sequence of the HsRad52 gene (10, 12). For PCR, 0.5 μg of DNA was used in mixture containing each primer at 200 nM, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1 mM MgCl2, 0.01% gelatin, each of the four dNTP's at 200 μM and 2.5 units of AmpliTaq ploymerase. The reaction mixture was heated at 95°C for 3 min and used in a PCR consisting of 30 cycles of 94°C for 1 min, 60°C for 1 min, and 72°C for 1 min. The resulting DNA fragment was labeled with [-32P] dCTP by random priming (24) and used as a probe for isolation of a HsRad52 clone from human testis cDNA library in lambda Charon BS phage (25). DNA isolated from a hybridization-positive clone was digested by Not I and treated with T4 DNA ligase. The ligation mixture was used for transformation of E. coli SY204. Ampicilin resistant transformants contained a plasmid, designated pEG970, which carries HsRad52 cDNA. The plasmid was used as a template for amplification of the coding region of HsRad52 gene by PCR reaction. The reaction was carried out by using Expand High Fidelity PCR Kit and primers EG182 and EG225. The resulting DNA fragment was inserted into expression vector pQE-31 in frame with 5' end sequence coding for a series of six histidine residues that function as a metal-binding domain in the translated fusion protein.–

On page 31, immediately preceding the claims, the enclosed Sequence Listing was added to the text.

In the Claims:

2. (Amended) A composition according to claim 1 wherein [said complex is capable of mediating the annealing of] said first and second nucleic acids are perfectly [to a] complementary [second single stranded nucleic acid] to each other.

5. (Amended) A composition according to claim 1 [further comprising a second single stranded] wherein said first and second nucleic acids [complexed with isolated Rad52 protein from a higher eukaryote] are minimally complementary to each other.

6. (Amended) A composition according to claim 1, 2, 5 or 23 [further comprising a second single stranded nucleic acid complexed with isolated Rad52 protein from a higher eukaryote] wherein at least one of said first and second nucleic acids are labeled.

Pending Claims 1-6, 14, 16-26 and 28 as Amended

1. (Amended) A composition comprising:

a) a first single stranded nucleic acid;

b) a second single stranded nucleic acid, wherein said first and second nucleic acids are complementary to each other; and

c) at least one recombinant Rad52 protein from a higher eukaryote.

2. (Amended) A composition according to claim 1 wherein said first and second nucleic acids are perfectly complementary to each other.

3. (Amended) A composition according to claim 1, 2, 5 or 23 wherein said Rad52 protein is labeled.

4. A composition according to claim 1 wherein said Rad52 is a human Rad 52 protein.

5. (Amended) A composition according to claim 1 wherein said first and second nucleic acids are minimally complementary to each other.

6. (Amended) A composition according to claim 1, 2, 5 or 23 wherein at least one of said first and second nucleic acids are labeled.

14. (Amended) A method of screening for a bioactive agent involved in nucleic acid binding comprising:

a) contacting:

i) a candidate bioactive agent;

ii) a first single stranded nucleic acid; and

iii) isolated Rad52 protein from a higher eukaryote; and

b) screening for binding of said candidate agent and said Rad52 to said first nucleic acid.

16. (Amended) A method of screening for a bioactive agent involved in nucleic acid binding comprising:

a) adding:

i) a candidate bioactive agent;

ii) a first single stranded nucleic acid; and

iii) isolated Rad52 protein from a higher eukaryote to form a mixture; and

b) screening said mixture for altered [biological] nucleic acid binding activity, when compared to the nucleic acid binding activity of said composition in the absence of said candidate agent.

17. (Amended) The method according to claim 14, 16, 18, 19, or 20 wherein said first nucleic acid and said isolated Rad52 are complexed prior to the addition of said candidate agent.

18. A method of screening for a bioactive agent involved in nucleic acid annealing comprising:

a) adding:

i) a candidate bioactive agent;

ii) a first single stranded nucleic acid; and

iii) isolated Rad52 protein from a higher eukaryote to form a mixture; and

b) screening said mixture for altered nucleic acid annealing activity, when compared to the nucleic acid annealing activity of said composition in the absence of said candidate agent.

19. A method of screening for a bioactive agent involved in strand exchange comprising:

a) adding:

i) a candidate bioactive agent;

ii) a first single stranded nucleic acid; and

iii) isolated Rad52 protein from a higher eukaryote to form a mixture; and

b) screening said mixture for altered strand exchange activity, when compared to the strand exchange activity of said composition in the absence of said candidate agent.

20. A method of screening for a bioactive agent involved in homology scanning comprising:

a) adding:

i) a candidate bioactive agent;

ii) a first single stranded nucleic acid; and

iii) isolated Rad52 protein from a higher eukaryote to form a mixture; and

b) screening said mixture for altered homology scanning activity, when compared to the homology scanning activity of said composition in the absence of said candidate agent.

21. The method according to claim 14, 16, 18, 19, or 20 wherein said Rad52 protein is mammalian Rad52 protein.

22. The method according to claim 21 wherein said Rad52 protein is human Rad52 protein.

23. A composition according to claim 1 wherein said first and second nucleic acids are substantially complementary to each other.

24. A composition according to claim 1 further comprising Rad51.

25. A composition according to claim 1 further comprising RPA.

26. A composition according to claim 1 wherein said Rad52 protein is at least 90% homologous to about amino acid 36 to about amino acid 185 of human Rad52 protein.

28. The method according to claim 14, 16, 18, 19, or 20 wherein said Rad52 protein is labeled.